

### REMARKS

Claims 71-134 are pending. Initially, Applicants note that there appears to be a typographical error in the Examiner's grouping of the claims. Claim 126 clearly belongs to Group II instead of Group III. Therefore, confirmation of the correct grouping of claims is requested from the Examiner.

Applicants elect with traverse Group II (claims 90-126 and 132-134) for examination on the merits. There would be no serious burden if all claims were examined in this application. Claim amendments are supported by the original disclosure and do not add new matter. They correct informalities and do not affect the scope of the claims. Applicants reserve the right to prosecute the non-elected subject matter in a further patent application. Further, under the Notice dated March 26, 1996 (1184 OG 86), Applicants request rejoinder of the non-elected method claims upon an indication that an elected product claim is allowable.

In satisfaction of their duties of candor and good faith, Applicants bring to the attention of the Examiner the related subject matter in Application Nos. 09/738,879, 09/950,003, 10/240,606, 10/274,706, 10/484,883, 10/496,037, 10/518,229, 10/518,303, 10/582,687, 10/868,359, 10/902,285, 11/030,156 and 11/440,749. She is invited to consider their prosecution histories in this application. The file wrappers of most, if not all, of these applications are accessible electronically so resubmission of those papers here would be redundant. But, if the Examiner prefers, Applicants would resubmit them in this application.

#### Inventive Concept

All claims of Groups I-III require the core structure (A), given in paragraph [0007] of US 2006/0014718, which has been modified by removal of the N-acetyl group and introduction of a N-sulfate group, by partial C5-epimerization and by optional depolymerization to give an optionally depolymerized epiK5-N-sulfate. These operations are described in detail in the specification as filed. Starting from these optionally depolymerized epiK5-N-sulfates, all the compounds of Groups I-III are prepared according to an inventive concept directed to the preparation of epiK5-N,O-oversulfates

having a molecular weight of from 2,000 to 45,000 and a sulfation degree higher than 4 by three simple reactions see (claim 71): (1) preparation of the quaternary salt of said optionally depolymerized epiK5-N-sulfate under precise conditions; (2) oversulfation of the quaternary salt to give optionally depolymerized, novel epiK5-amine-O-oversulfates having a sulfation degree of from 3.55 to 3.8 see (Claim 110) and (3) N-sulfation thereof to give the desired, novel epiK5-N,O-sulfate-derivatives see (Claim 90).

In order to prepare low molecular weight epiK5-N,O-sulfates as required in claim 90, depolymerized epiK5-N-sulfates which were unknown at the filing date of the present application had to be provided.

The members of Groups I-III are closely related, such that a search and examination of the entire group of claims can be made without serious burden. The Examiner can examine all the claims of the three groups on the merits, even though they may be directed to independent and distinct inventions in the same inventive concept.

Applicant submit that claims 71-116 and 132-134 are the whole of a sole inventive concept because all the products of claims 90-116 and 132-134 are prepared according to the process of claims 71-89 starting from the products of claims 117-126 as obtained according to claims 127-131. They are antiviral agents (see paragraphs [0037] and [0038] and copending application 10/518,303 claiming pharmaceutical compositions comprising the present compounds of claims 110-116 which also are intermediates in the process of claim 71).

In practice, in all claims of Groups I-III involve the N-deacetylated/N-sulfated, C5-epimerized and optionally depolymerized, core repetitive structure (A) bearing sulfate groups on the amino group, on hydroxyl groups or both of the amino and hydroxyl groups.

#### Special Technical Feature

Applicants submit that the whole subject matter of Groups I-III is completely different from the subject matter disclosed by the cited Oreste et al. reference.

An objective of the invention was the preparation of epiK5-N,O-oversulfate-

derivatives having very high degree sulfation, i.e. N-deacetylated, N-sulfated, O-sulfated C5-epimerized K5 polysaccharides having an average molecular weight within a broad range and a degree of sulfation as high as possible. According to their inventive concept, Applicants aimed to provide highly anionic products which could be useful as antiangiogenetic and antiviral agents they could also be used as drugs in other disorders, where the use of heparin would cause side effects due of its anticoagulant action (see paragraphs [0006], [0033], [0034] and [0037] of this published application). Applicants ultimately succeeded in finding such epiK5-N,O-oversulfate-derivatives having a sulfation degree higher than 4 after solving three main problems which are closely interrelated.

Problem 1. Preparation of the epiK5-N,O-oversulfate-derivatives. At the effective filing date of the present application, the known prior art did not disclose N-deacetylated, N,O-sulfated K5 polysaccharides (epimerized or not epimerized) having a sulfation degree higher than 3.2. According to Applicants, this sulfation degree was not sufficient to assure a good radical scavenging and antiviral activity, but the known prior art neither disclosed nor suggested a method for attaining such a high degree of sulfation.

Problem 2. Preparation of very highly O-sulfated epiK5-amine-derivatives. Notwithstanding the disclosure of Oreste et al US 2002/0062019, wherein it is stated that by oversulfation of epiK5-N-sulfate an oversulfated product (now designated epiK5-amine-O-oversulfate) having a content of sulfates per disaccharide of 2-3.5 is obtained (see paragraph [0073] of '019), Applicants observed that under the oversulfation conditions of '019 a sulfation higher than 3.2 was not obtainable (see paragraph [0013] of this published application). On the other hand, the <sup>13</sup>C-NMR spectrum given in Figure 7 of '019 shows that the sulfation degree of the "oversulfated compound" of Example 1(d) of '019 is about 3.1, thus confirming that epiK5-amine-O-oversulfate-derivatives having a sulfation degree higher than 3.1-3.2 were not described in the known prior art at the effective filing date of the present application.

This problem has been solved by allowing the tertiary or quaternary organic salt of the starting epiK5-N-sulfate derivative to stay at pH 7 for 30-60 minutes, as set forth

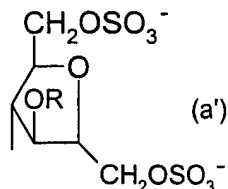
in the first paragraph of the Summary of the Invention, throughout the description and in claim 1, step (a).

Problem 3. Preparation of very highly O-sulfated epiK5-amine-derivatives in a broad range of molecular weight and consequent availability of low molecular weight epiK5-N-sulfates free of acetyl groups and easily obtainable. These products were unknown at the effective filing date of the present application. This problem has been solved by finding a method for the nitrous depolymerization of K5-N-sulfate and of epiK5-N-sulfate capable of giving new low molecular weight products in a very wide, mean low molecular weight. This method is well detailed in the specification as filed.

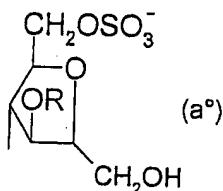
The special technical feature of the subject matter of claims 71-134 resides in that:

- (a) the present application describes a process wherein
  - (a1) in step (a), the quaternary salt of the optionally depolymerized epiK5-N-sulfate is prepared under specific conditions not disclosed by Oreste et al.;
  - (a2) in step (b) epiK5-amine-O-oversulfate-derivatives are obtained, having a sulfation degree of from 3.55 to 3.8, not disclosed by Oreste et al.; and
  - (a3) in step (c), the obtained epiK5-amine-O-oversulfate-derivatives are directly subjected to a N-sulfation, while this direct step is not provided by Oreste et al.
- (b) the present application discloses low molecular weight epiK5-N-sulfates and Oreste et al. do not;
- (c) the present application discloses epiK5-amine-O-oversulfate-derivatives having a sulfation degree of from 3.55 to 3.8 and Oreste et al. do not (the maximal degree of sulfation is 3.1-3.2);
- (d) the present application discloses epiK5-N,O-oversulfate-derivatives having a sulfation degree higher than 4 and Oreste et al. do not (the maximal degree of sulfation is 2.9);
- (e) the present application discloses epiK5-N,O-oversulfate-derivatives having a sulfation degree higher than 4 and practically devoid of anticoagulant activity while, on the contrary, the products of Oreste et al. are powerful anticoagulant and antithrombotic agents;

(f) the depolymerized compounds of claims 90-116 obtained according to claims 71-89 are all characterized by the structure (a')

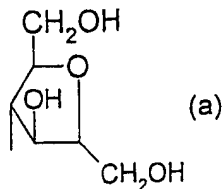


in the majority of their chains while the compounds disclosed by Oreste et al. are not and cannot be characterized by the structure (a'). Even though Oreste et al. do not give any structure of the depolymerized, LMW-epiK5-N,O-sulfates they have prepared, the skilled in the art knows that said depolymerized products are characterized by the structure (a°)



in the majority of their chains; and

(g) the starting materials in the preparation of the LMW-epiK5-amine-O-oversulfates (degree of sulfation of from 3.55 to 3.8) and of LMW-epiK5-N,O-oversulfates (degree of sulfation higher than 4) of claims 90-116 obtained according to claims 71-89 are all characterized by the structure (a)



while the starting materials in the preparation of the LMW-epiK5-N,O-sulfates (degree of sulfation of from 2.3 to 2.9) described by Oreste et al. are not and cannot be characterized by the structure (a) in the majority of their chains. Even though the extremity of the chain is not given in the Oreste et al. cited document, the skilled in the art knows that said starting materials are characterized by a sulfated uronic or glucosamine subunit of the repetitive disaccharide.

Thus the technical feature of the groups I-III is completely different, in all of its aspect, to the disclosure of the prior art and Groups I-III are so closely related (differently sulfated repetitive disaccharide units), that a search and examination of the entire claim should be made without serious burden. Furthermore, Groups I-III are closely linked each other by an inseparable "new starting material-new intermediate-new final product" relationship in a "new process".

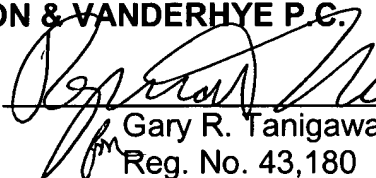
In conclusion, in electing Group II with traverse, Applicants require that the Examiner examine the whole set of claims as a sole inventive concept, closely linking Groups I-III which decidedly differentiate themselves from the prior art.

Applicants earnestly solicit an early and favorable examination on the merits. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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